

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberein, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

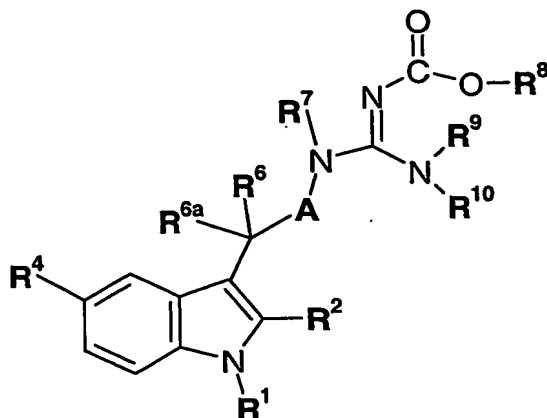
GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists:  
WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185, WO 00/53602, WO 02/066477, WO 02/066478, WO 02/06645 and WO 02/092565.

It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),

- 2 -



Formula (I)

wherein

A represents a direct bond or optionally substituted C<sub>1-5</sub>alkylene;

5 **R**<sup>1</sup> represents hydrogen; optionally substituted C<sub>1-8</sub>alkyl; or (CH<sub>2</sub>)<sub>b</sub>-**R**<sup>a</sup>, wherein

**R**<sup>a</sup> represents C<sub>3-8</sub>cycloalkyl and b is zero or an integer from 1 to 6;

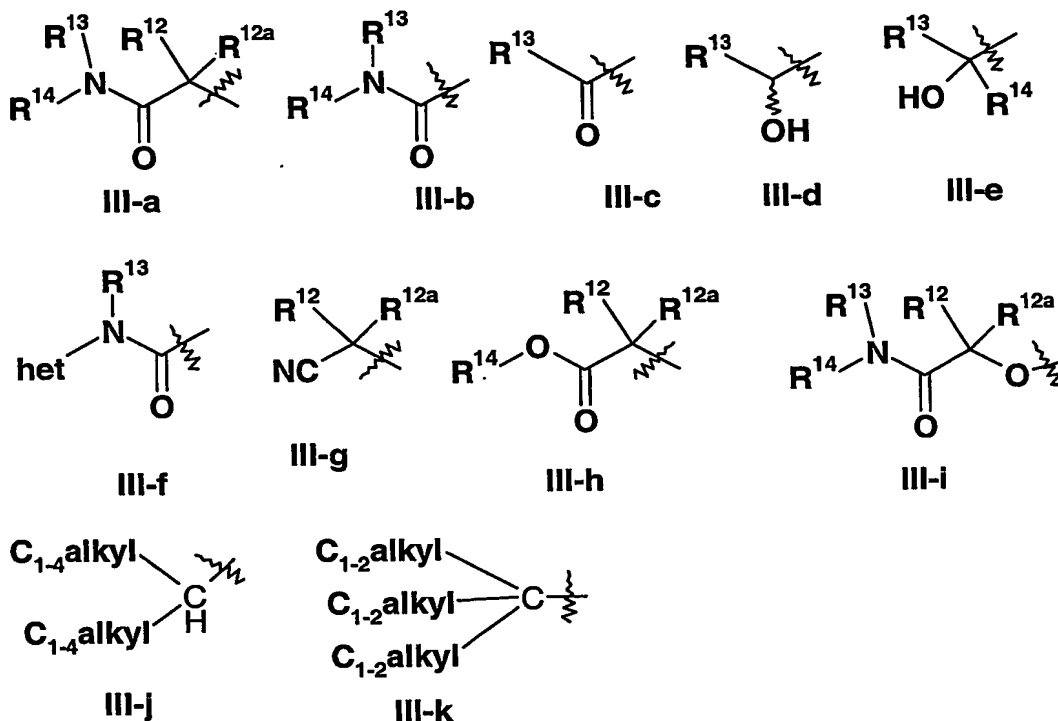
**R**<sup>2</sup> represents an optionally substituted mono- or bi-cyclic aromatic ring structure wherein the optional substituents are selected from cyano, NR<sup>3</sup>R<sup>3a</sup>, optionally substituted C<sub>1-8</sub>alkyl, optionally substituted C<sub>1-8</sub>alkoxy or halo;

10 **R**<sup>3</sup> and **R**<sup>3a</sup> are independently selected from hydrogen; optionally substituted C<sub>1-8</sub>alkyl and optionally substituted aryl;

**R**<sup>4</sup> is selected from optionally substituted C<sub>1-6</sub>alkoxy, an optionally substituted 3- to 8-membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; or a group of formula **III-a**; **III-b**; **III-c**; **III-d**; **III-e**; **III-f**, **III-g**,


15 **III-h**, **III-i**, **III-j** or **III-k**;

- 3 -



wherein **het** represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$R^6$  and  $R^{6a}$ , are selected from:

- 5 (i)  $R^6$  and  $R^{6a}$  are independently selected from hydrogen and optionally substituted  $C_{1-8}$ alkyl; or
- (ii)  $R^6$  and  $R^{6a}$  together represent carbonyl; or
- (iii)  $R^6$    $A-N-R^7$  represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, and  $R^{6a}$  represents hydrogen and optionally substituted  $C_{1-8}$ alkyl;

$R^7$  represents hydrogen or optionally substituted  $C_{1-8}$ alkyl;

$R^8$  are selected from: :  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl and heterocyclyl wherein  $R^8$  is optionally substituted with halo, hydroxy, amino,  $NO_2$ , cyano,  $C_{1-4}$ alkanoyloxy,

- 15 N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino, HO- $C_{2-4}$ alkyl-NH-, HO- $C_{2-4}$ alkyl-N( $C_{1-4}$ alkyl)-, -S( $O_n$ )- $C_{1-4}$ alkyl, -N( $R$ )S( $O_n$ )- $C_{1-4}$ alkyl, -S( $O_n$ )N( $R$ )- $C_{1-4}$ alkyl or heterocyclyl optionally substituted by  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl or  $C_{2-4}$ alkynyl, wherein  $R$  is hydrogen or  $C_{1-4}$ alkyl;

- 4 -

$R^9$  is selected from:

- (i)  $R^9$  represents hydrogen, aryl, a 3- to 10 membered heterocyclic ring or optionally-substituted  $C_{1-8}$ alkyl; and
- (ii) the structure  $N(R^9R^{10})$  represents an optionally-substituted 3- to 10 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

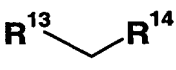
$R^{10}$  meets the definition in option (ii) for  $R^9$  above or when  $R^9$  meets the definition in option (i) above  $R^{10}$  represents hydrogen or optionally substituted  $C_{1-8}$ alkyl;

$R^{12}$  and  $R^{12a}$  are selected from:

- (i)  $R^{12}$  and  $R^{12a}$  are independently selected from hydrogen or optionally substituted  $C_{1-8}$ alkyl; or
- (ii)  $R^{12}$  and  $R^{12a}$  together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

$R^{13}$  and  $R^{14}$  are selected from:

- (i)  $R^{13}$  is selected from hydrogen; optionally substituted  $C_{1-8}$ alkyl; optionally substituted aryl;  $-R^d-Ar$ , where  $R^d$  represents  $C_{1-8}$ alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and  $R^{14}$  is selected from hydrogen; optionally substituted  $C_{1-8}$ alkyl and optionally substituted aryl;
- (ii) wherein  $R^4$  represents a group of formula III-a, III-b or III-i, then the group  $NR^{13}(-R^{14})$  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

- (iii) wherein  $R^4$  represents structure III-e,  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

$n$  is 0 to 2;

or a salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

- 5 -

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of a compound of Formula (I), or salt, pro-drug or solvate thereof:

- (a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;
- (b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and
- (c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a compound of Formula (I), or salt, pro-drug or solvate thereof, to a patient.

- Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

Whilst the invention comprises compounds of the invention, and salts, pro-drugs or solvates thereof, in a further embodiment of the invention, the invention comprises compounds of the invention and salts thereof.

In the present specification, unless otherwise indicated, an **alkyl**, **alkylene** or **alkenyl** moiety may be linear or branched.

The term "**alkylene**" refers to the group  $-\text{CH}_2-$ . Thus,  $\text{C}_8$  alkylene for example is  $-(\text{CH}_2)_8-$ .

The term "**aryl**" refers to phenyl or naphthyl.

The term "**carbamoyl**" refers to the group  $-\text{CONH}_2$ .


The term "**halo**" refers to fluoro, chloro, bromo or iodo.

The term "**heterocyclyl**" or "**heterocyclic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring or a 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring

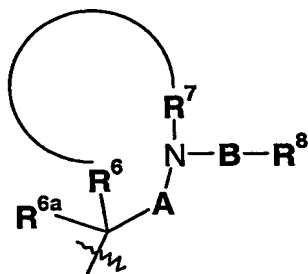
- 6 -

- nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Examples of saturated or partially saturated heterocyclic rings include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O<sub>2</sub>) group.
- The term "aromatic ring" refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include phenyl, thienyl and pyridyl.

The symbol  denotes where the respective group is linked to the remainder of the molecule.

- For the avoidance of doubt, when  $R^6$    $A-N-R^7$  together form an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, then the groups shown cyclise to form a nitrogen-containing heterocyclic ring, i.e

- 7 -



, optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S.

Examples of **C<sub>1-8</sub>alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; example of **C<sub>1-8</sub>alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of **C<sub>1-8</sub>alkoxy** include methoxy, ethoxy and butyloxy; examples of **C<sub>1-4</sub>alkanoyloxy** include formyloxy, propanoyloxy and butanoyloxy, examples of **N-C<sub>1-4</sub>alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C<sub>1-4</sub>alkylamino**, examples of **HO-C<sub>2-4</sub>alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropylamino, examples of **HO-C<sub>2-4</sub>alkyl-N(C<sub>1-4</sub>alkyl)** include N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropylamino.

It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

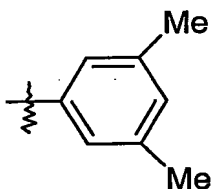
Preferred compounds of Formula (I) are those wherein any one of the following or a combination of the following apply.

- 8 -

Preferably A represents optionally substituted C<sub>1-5</sub>alkylene. Further preferably C<sub>1-4</sub>alkylene. Most preferably methylene or ethylene.

Preferably R<sup>1</sup> represents hydrogen or optionally substituted C<sub>1-6</sub>alkyl. More preferably R<sup>1</sup> represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably R<sup>1</sup> represents hydrogen.

- 5 Preferably R<sup>2</sup> represents an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano, NR<sup>e</sup>R<sup>f</sup>, optionally substituted C<sub>1-8</sub>alkyl (preferably, C<sub>1-4</sub>alkyl, eg, methyl or ethyl), optionally substituted C<sub>1-8</sub>alkoxy (preferably, C<sub>1-6</sub>alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein R<sup>e</sup> and R<sup>f</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl or aryl. Further preferably R<sup>2</sup>
- 10 is optionally substituted phenyl wherein the optional substituents are selected from cyano, NR<sup>e</sup>R<sup>f</sup>, optionally substituted C<sub>1-4</sub>alkyl, optionally substituted C<sub>1-6</sub>alkoxy, F, Br or Cl wherein R<sup>e</sup> and R<sup>f</sup> are as defined above. Yet further preferably R<sup>2</sup> is optionally substituted phenyl wherein the optional substituents are selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably R<sup>2</sup> represents



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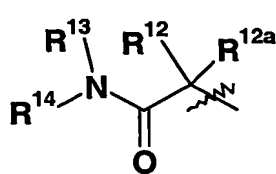
wherein Me represents methyl. Preferably R<sup>2</sup> bears 1, 2 or 3 substituents.

Preferably R<sup>3</sup> and R<sup>3a</sup> are independently selected from hydrogen; optionally substituted C<sub>1-6</sub>alkyl and , optionally substituted aryl . Further preferably R<sup>3</sup> and R<sup>3a</sup> are independently selected from methyl, ethyl, *tert*-butyl and phenyl.

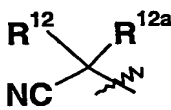


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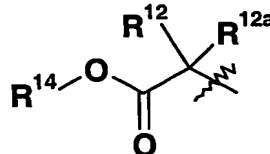
Preferably  $R^4$  is selected from a group of formula III-a, III-g, III-h, III-i, III-j or III-k:



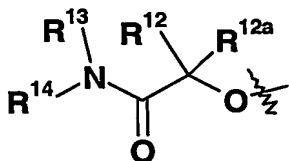
III-a



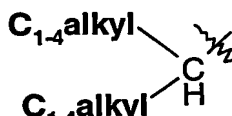
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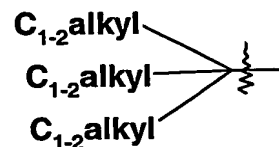
III-h



III-i

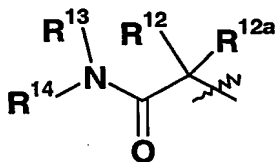


III-j



III-k

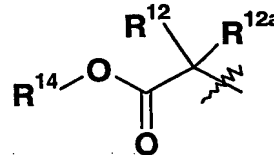
Further preferably  $R^4$  is selected from one of the following groups:



III-a



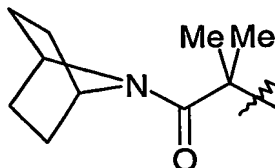
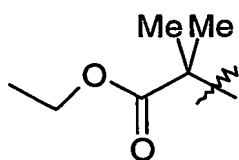
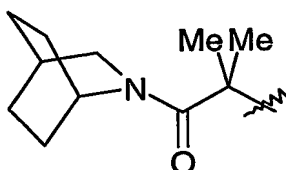
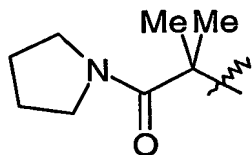
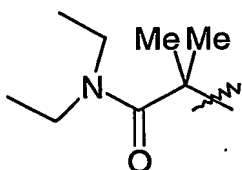
III-g



III-h

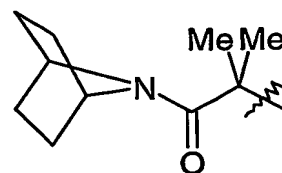
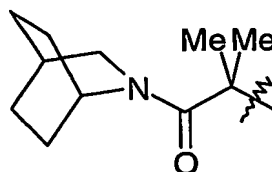
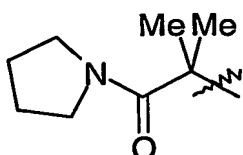
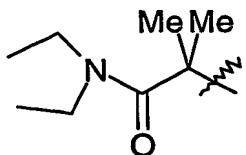
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Yet further preferably  $R^4$  is selected from one of the following groups:



wherein Me represents methyl.

Most preferably  $R^4$  is selected from one of the following groups:



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In one embodiment,  $R^6$  and  $R^{6a}$  each represent hydrogen and A represents  $C_{1-4}$ alkylene (preferably methylene).

In a further embodiment of the invention  $R^6$  represents hydrogen,  $R^{6a}$  represents methyl,  
5 and A represents  $C_{1-4}$ alkylene (preferably methylene).

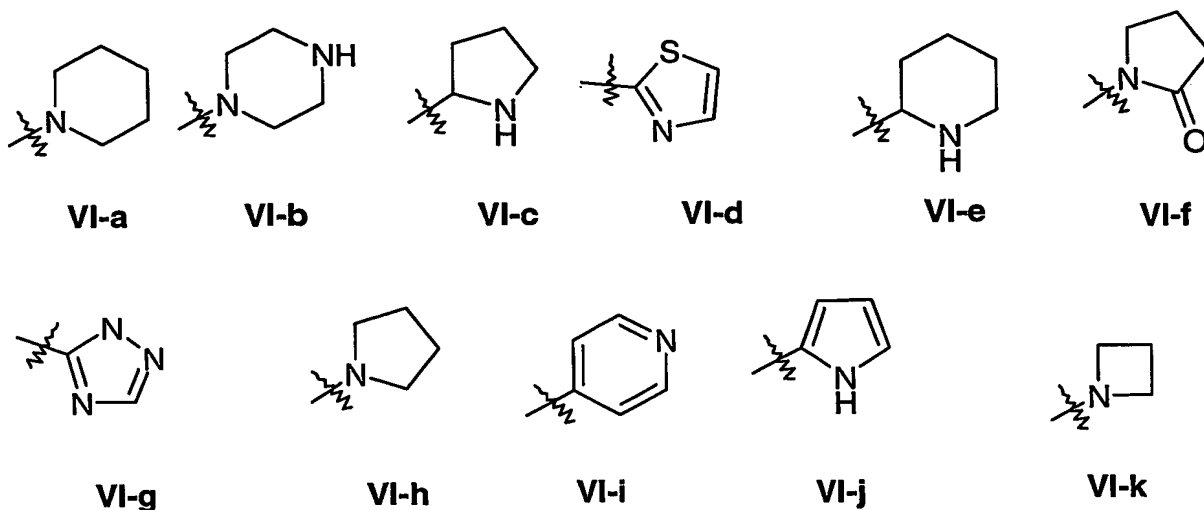
Preferably  $R^7$  is selected from hydrogen or optionally-substituted  $C_{1-6}$ alkyl. Further preferably  $R^7$  represents hydrogen, methyl, ethyl or *tert*-butyl.

Preferably  $R^8$  is selected from:  $C_{1-4}$ alkyl optionally substituted by heterocyclyl,  $C_{1-4}$ alkanoyloxy $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyloxy, wherein heterocyclyl is optionally substituted  
10 by  $C_{1-4}$ alkyl. Preferably  $C_{1-4}$ alkyl or  $C_{1-4}$ alkyl substituted by heterocyclyl wherein heterocyclyl is optionally substituted by methyl or  $C_{1-4}$ alkanoylamino. Most preferably ethyl, isopropyl, n-butyl, 5-methyl-2-oxo-1,3-dioxol-4-ylmethyl or 1-oxoethoxy-(1,1,-dimethyl-ethyl).

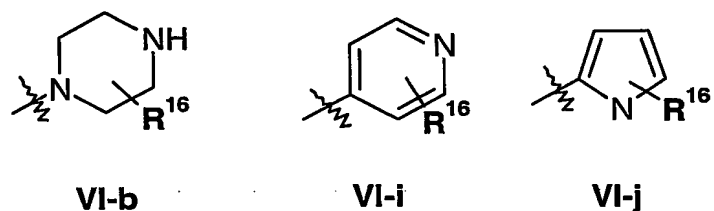
Preferably  $R^9$  comprise part of the heterocyclic ring formed by  $N(R^9R^{10})$  or is  
15 hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally substituted  $C_{1-4}$ alkyl wherein the optional substituents on  $C_{1-4}$ alkyl, aryl or a heterocyclic ring are selected from: hydroxy, amino, nitro, cyano, optionally-substituted aryl, optionally substituted 3- to 8- membered heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S,  $-O-R^b$ ,  $C(O)NR^bR^c$ ,  
20  $-NR^bR^c$ ,  $-NR^cC(O)-R^b$ ,  $-C(O)NR^bR^c$ ,  $-NR^cS(O_{0-2})R^b$ ,  $-S(O_{0-2})R^b$ , wherein  $R^b$  and  $R^c$  are as defined above. .

When  $R^9$  is a  $C_{1-6}$ alkyl group substituted by an optionally-substituted 3 to 10 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S, the heterocyclic ring is preferably selected from pyridyl, thienyl, piperidinyl, imidazolyl,  
25 triazolyl, thiazolyl, pyrrolidinyl, piperazinyl, morpholinyl, imidazolinyl, benztriazolyl, benzimidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl, furanyl, pyrrolyl, 1,3-dioxolanyl, 2-azetanyl, each of which is optionally substituted. Further preferably a group of formula VI-a, VI-b, VI-c, VI-d, VI-e, VI-f, VI-g, VI-h, VI-i, VI-j or VI-k:, wherein each group is optionally substituted by one or more groups selected from  $R^{16}$  on ring carbon atoms  
30 or ring heteroatoms where chemically feasible

- 11 -



Most preferably a group of formula **VI-b**, **VI-i** or **VI-j**:



5 wherein

$R^{16}$  represents hydrogen, aryl, a 3- to 10 membered heterocyclic ring or optionally substituted  $C_{1-4}$ alkyl wherein the optional substituents are selected from: hydroxy, amino, nitro, cyano, optionally-substituted phenyl, optionally substituted 3- to 8- membered heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S,  $-O-R^b$ ,  $C(O)NR^bR^c$ ,  $-NR^bR^c$ ,  $-NR^cC(O)-R^b$ ,  $-C(O)NR^bR^c$ ,  $-NR^cS(O_{0-2})R^b$ ,  $-S(O_{0-2})R^b$ , wherein  $R^b$  and  $R^c$  are as defined above;

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In a further embodiment of the invention  $R^9$  is  $C_{1-4}$ alkyl optionally substituted by cyano, preferably cyanopropyl.

Preferably  $R^{10}$  comprises part of the heterocyclic ring formed by  $N(R^9R^{10})$  or  $R^{10}$  is hydrogen or optionally substituted  $C_{1-6}$ alkyl. Further preferably  $R^{10}$  comprises part of the heterocyclic ring formed by  $N(R^9R^{10})$  or  $R^{10}$  is selected from: hydrogen, methyl, ethyl or *iso*-propyl. Most preferably  $R^{10}$  is hydrogen or comprises part of the heterocyclic ring formed by  $N(R^9R^{10})$ .

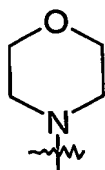
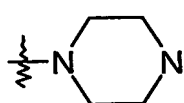
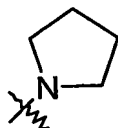
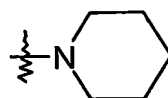
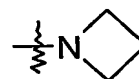
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When  $N(R^9R^{10})$  represent an optionally substituted 3- to 10- membered heterocyclic ring,  $N(R^9R^{10})$  is preferably selected from a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatom independently selected from O, N and S.

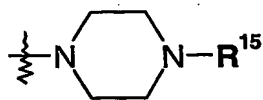
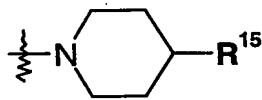
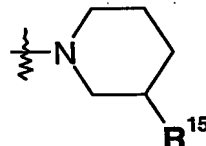
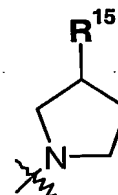
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- 12 -

Further preferably a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatom independently selected from O, N and S selected from pyrrolidinyl, thienyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl piperazinyl, imidazole, azetidiny or azetiny. Further preferably the structure  $N(R^9R^{10})$  is a heterocyclic ring selected from an optionally-substituted group of formula, **IV-a**, **IV-b**, **IV-c**, **IV-d** and **IV-e**, wherein the optional substituents are preferably selected from the groups listed for  $R^{15}$  below

**IV-a****IV-b****IV-c****IV-d****IV-e**

Further preferably the structure  $N(R^9R^{10})$  is selected from a group of formula **Va**, **Vb**, **Vc** or **Vd**:

**V-a****V-b****V-c****V-d**

Most preferably the structure  $N(R^9R^{10})$  is a group of formula **V-c**:

$R^{15}$  represents hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally substituted  $C_{1-4}$ alkyl wherein the optional substituents on aryl, a heterocyclic ring or  $C_{1-6}$ alkyl are selected from: hydroxy, amino, nitro, cyano, optionally-substituted aryl, optionally substituted 3- to 8- membered heterocycl containing from 1 to 4 heteroatoms independently selected from O, N and S,  $-O-R^b$ ,  $C(O)NR^bR^c$ ,  $-NR^bR^c$ ,  $-NR^cC(O)-R^b$ ,  $-C(O)NR^bR^c$ ,  $-NR^cS(O_{0-2})R^b$ ,  $-S(O_{0-2})R^b$ , wherein  $R^b$  and  $R^c$  are as defined above. Preferably  $R^{15}$  is heterocycl. Further preferably  $R^{15}$  is selected from: pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl or thiazolyl. Most preferably  $R^{15}$  is pyridyl.

In a further embodiment of the invention  $R^{15}$  is selected from pyridyl or  $C_{1-4}$ alkyl.

Further preferably pyridyl or methyl.

- 13 -

In a further embodiment of the invention  $N(R^9R^{10})$  represent an optionally substituted 3- to 10- membered heterocyclic ring, wherein the optional substituents are selected from  $R^{15}$  as defined above.

Preferably  $R^{12}$  and  $R^{12a}$  are independently selected from: hydrogen, optionally substituted  $C_{1-6}$ alkyl or  $R^{12}$  and  $R^{12a}$  together with carbon to which they are attached from an optionally substituted 3- to 6-membered cycloalkyl ring. Further preferably  $R^{12}$  and  $R^{12a}$  are independently selected from: hydrogen, methyl, ethyl or *tert*-butyl. Most preferably  $R^{12}$  and  $R^{12a}$  are both methyl.

Preferably  $R^{13}$  and  $R^{14}$ , are independently selected from hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted phenyl and  $-R^d$ -phenyl, where  $R^d$  represents  $C_{1-6}$ alkylene or and an optionally substituted 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 3 (preferably 1 or 2) further heteroatoms independently selected from O, N and S. Further preferably  $R^{13}$  and  $R^{14}$ , are independently selected from hydrogen or  $C_{1-6}$ alkyl.

Where optional substitution is mentioned at various places, this refers to one, two, three or more optional substituents. Unless otherwise indicated above (ie, where a list of optional substituents is provided), each substituent can be independently selected from  $C_{1-8}$ alkyl (eg,  $C_{2-6}$ alkyl, and most preferably methyl, ethyl or *tert*-butyl);  $C_{3-8}$ cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxy;  $C_{1-6}$ alkoxy, preferably methoxy or  $C_{2-4}$ alkoxy; halo, preferably Cl or F;  $Hal_3C-$ ,  $Hal_2CH-$ ,  $HalCH_2-$ ,  $Hal_3CO-$ ,  $Hal_2CHO$  or  $HalCH_2O$ , wherein Hal represents halo (preferably F);  $R^gCH_2O-$ ,  $R^hC(O)N(R)-$ ,  $R^hSO_2N(R)-$  or  $R^g-R^hN-$ , wherein  $R^g$  and  $R^h$  independently represent hydrogen or  $C_{1-8}$ alkyl (preferably methyl or  $C_{2-6}$ alkyl or  $C_{2-4}$ alkyl), or  $R^g-R^hN-$  represents an optionally substituted  $C_{3-8}$ , preferably  $C_{3-6}$ , heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; hydrogen; or  $R^kC(O)O-$  or  $R^kC(O)-$ ,  $R^k$  representing hydrogen, optionally substituted phenyl or  $C_{1-6}$ alkyl (preferably methyl, ethyl, *iso*-propyl or *tert*-butyl). For optional substitution of the heterocyclic ring represented by  $R^g-R^hN-$ , at least one (eg, one, two or three) substituents may be provided independently selected from  $C_{1-6}$ alkyl (eg,  $C_{2-4}$ alkyl, more preferably methyl); phenyl;  $CF_3O-$ ;  $F_2CHO-$ ;  $C_{1-8}$ alkoxy, preferably methoxy, ethoxy or  $C_{3-6}$ alkoxy;  $C_{1-8}$ alkoxyC(O), preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or  $C_{3-6}$ alkoxyC(O)-; phenoxycarbonyl; phenoxy;  $C_{1-8}$ alkanoyl, preferably acetyl, ethanoyl or  $C_{3-6}$ alkylanoyl; carboxy;  $C_{1-8}$ alkylS(O)<sub>nn</sub> wherein nn is an

- 14 -

integer between 0 and 2, preferably methylthio, ethylthio, C<sub>3-6</sub>alkylthio, methylsulphinyl, ethylsulphinyl, C<sub>3-6</sub>alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C<sub>3-6</sub>alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); R<sup>m</sup>R<sup>n</sup>N- where R<sup>m</sup> and R<sup>n</sup> are independently hydrogen or C<sub>1-6</sub>alkyl (preferably C<sub>2-4</sub>alkyl, more preferably methyl, most preferably R<sup>m</sup>=R<sup>n</sup>=methyl); and  
 5 nitro.

Where optional substitution of a ring is mentioned at various places, this most preferably refers to one, two, three or more substituents selected from C<sub>1-8</sub>alkyl (eg, C<sub>2-6</sub>alkyl, and most preferably methyl); C<sub>1-8</sub>alkoxy, preferably methoxy, ethoxy or C<sub>3-6</sub>alkoxy; C<sub>1-8</sub>alkylS(O)<sub>nn</sub> wherein nn is an integer between 0 and 2, preferably methylthio, ethylthio,  
 10 C<sub>3-6</sub>alkylthio, methylsulphinyl, ethylsulphinyl, C<sub>3-6</sub>alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C<sub>3-6</sub>alkylsulphonyl; halo (eg, F, Cl or Br); cyano; and NO<sub>2</sub>.

A preferred group of compounds of the invention comprise compounds of Formula (I) wherein:

N(R<sup>9</sup>R<sup>10</sup>) represents an optionally-substituted 3- to 8- membered heterocyclic ring  
 15 optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S, preferably substituted by heterocyclyl;  
 or a salt, pro-drug or solvate thereof.

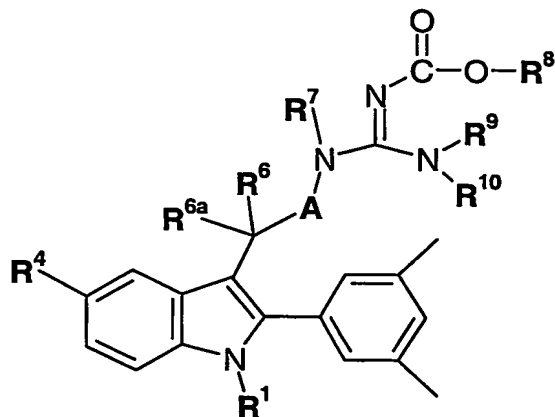
A preferred group of compounds of the invention comprise compounds of Formula (I) wherein:

20 R<sup>9</sup> is a C<sub>1-6</sub>alkyl group substituted by an optionally-substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; and

R<sup>10</sup> represents hydrogen or C<sub>1-6</sub>alkyl  
 or a salt, pro-drug or solvate thereof.

- 15 -

A preferred group of compounds of the invention comprises a compound of Formula (Ia):

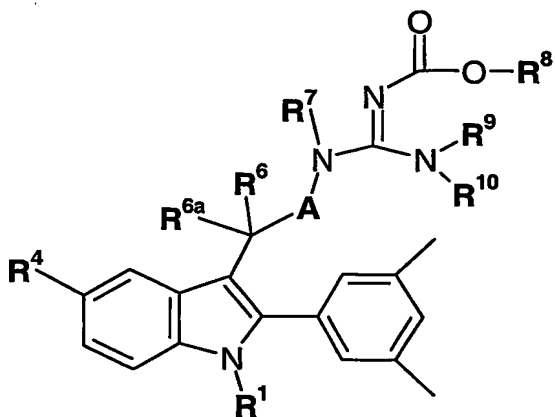


Formula (Ia)

5 wherein:

A, X,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{3a}$ ,  $R^6$ ,  $R^{6a}$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{12}$  and  $R^{12a}$  are as defined above;  
or a salt, pro-drug or solvate thereof.

A preferred group of compounds of the invention comprises a compound of Formula (Ib):

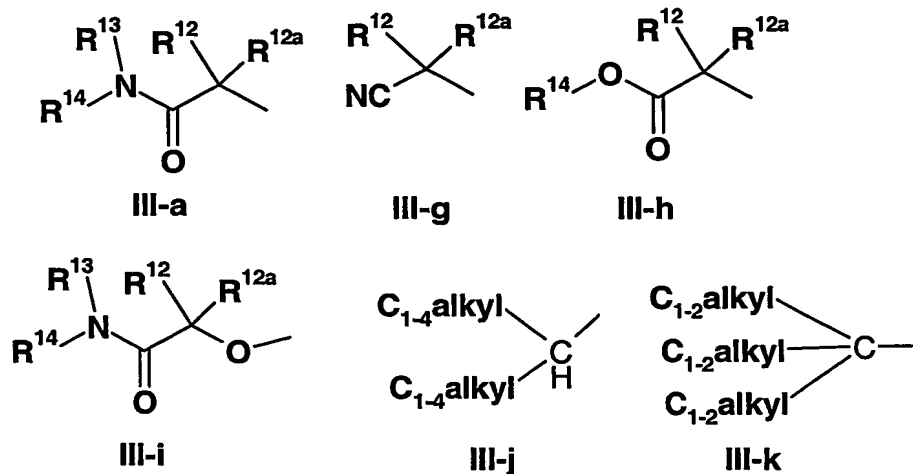


Formula (Ib)

10 wherein:

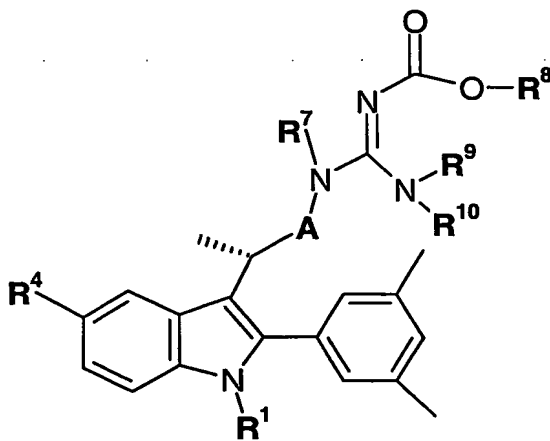
- 16 -

$R^4$  is selected from one of the following groups:



and A, X,  $R^1$ ,  $R^3$ ,  $R^{3a}$ ,  $R^6$ ,  $R^{6a}$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{12}$ ,  $R^{12a}$ ,  $R^{13}$ , and  $R^{14}$  are as defined above;  
or a salt, pro-drug or solvate thereof.

- 5 A further preferred group of compounds of the invention comprises a compound of Formula (Ic):



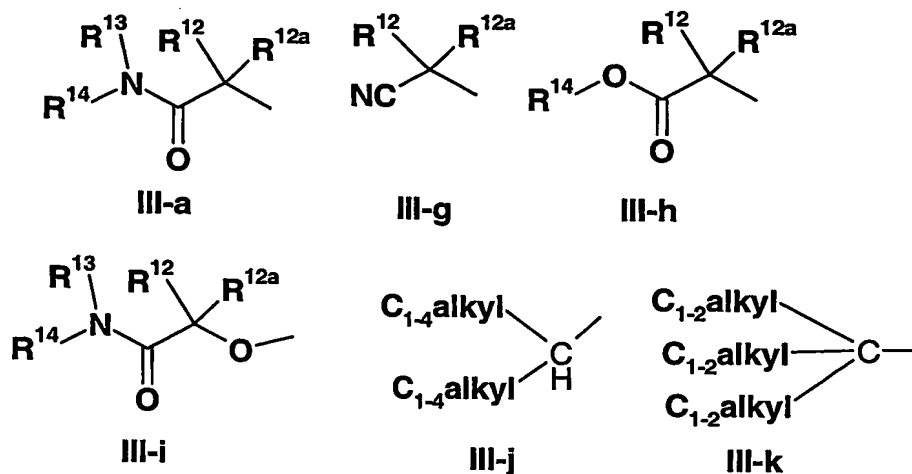
Formula (Ic)

wherein:



- 17 -

$R^4$  is selected from one of the following groups:

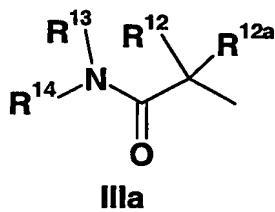


and A, X,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{3a}$ ,  $R^6$ ,  $R^{6a}$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{12}$ ,  $R^{12a}$ ,  $R^{13}$ , and  $R^{14}$  are as defined above;

5 or a salt, pro-drug or solvate thereof.

A yet further preferred group of compounds of the invention comprises a compound of Formula (Ia), (Ib) or (Ic) wherein:

$R^4$  is a group of Formula IIIa:



10  $NR^{13}(-R^{14})$  represents an optionally substituted 7- to 8- membered bicyclic heterocyclic ring and A, X,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{3a}$ ,  $R^4$ ,  $R^6$ ,  $R^{6a}$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{12}$  and  $R^{12a}$  are as defined above; or a salt, pro-drug or solvate thereof.

Particularly preferred compounds according to the present invention are wherein the compound is selected from:

15 isopropyl [(1*E*)-({(2*S*)-2-[5-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylene]carbamate;

isopropyl [(1*E*)-({(2*S*)-2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl}amino)(3-pyridin-4-ylpyrrolidin-1-

20 yl)methylene]carbamate; and

- 18 -

2-[[[(1*E*)-({(2*S*)-2-[5-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylene]amino}carbonyl)oxy]-2-methylpropyl acetate

or a salt, pro-drug or solvate thereof.

- 5 According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (Ia), Formula (Ib), Formula (Ic) or preferred compounds of the invention, or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the  
10 following uses of a compound of Formula (Ia), Formula (Ib), Formula (Ic) or preferred compounds of the invention, or salt, pro-drug or solvate thereof:

- (a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;
- (b) the use in the manufacture of a medicament for administration to a patient, for reducing  
15 the secretion of luteinizing hormone by the pituitary gland of the patient; and
- (c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

20 The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I).

Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

- 25 a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-  
30 191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

- 19 -

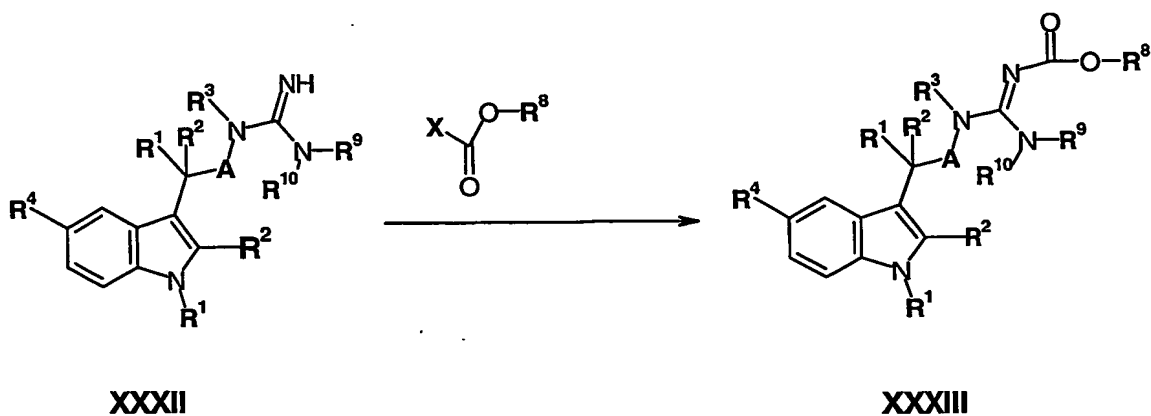
An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C<sub>1-6</sub>alkoxymethyl esters for example methoxymethyl, C<sub>1-6</sub>alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C<sub>3-8</sub>cycloalkoxycarbonyloxyC<sub>1-6</sub>alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1-6</sub>alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and  $\alpha$ -acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of  $\alpha$ -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

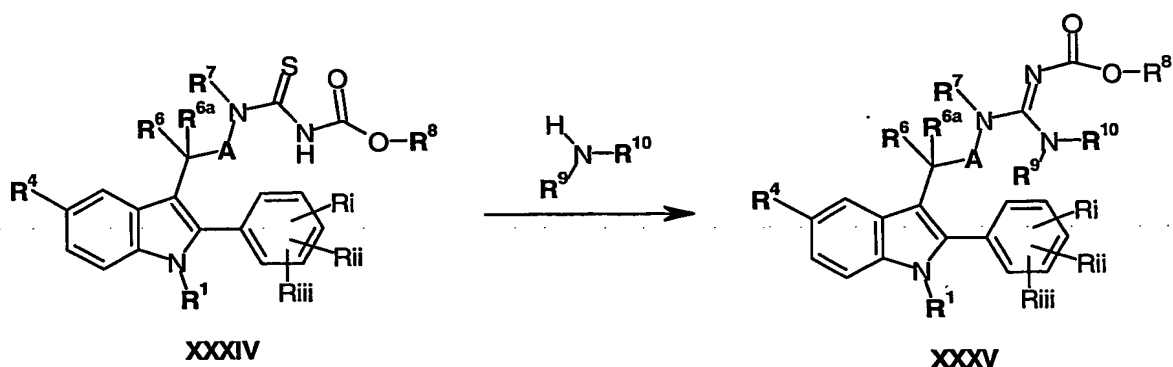
The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (b) as follows, these processes are provided as a further feature of the invention:-

(a) Reaction of a compound of formula XXXII as follows



wherein X is a leaving group;

(b) Reaction of a compound of Formula XXXIV as follows



5

and thereafter if necessary:

- i) converting a compound of the Formula (I) into another compound of the Formula (I);
- ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate.

10

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

15

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

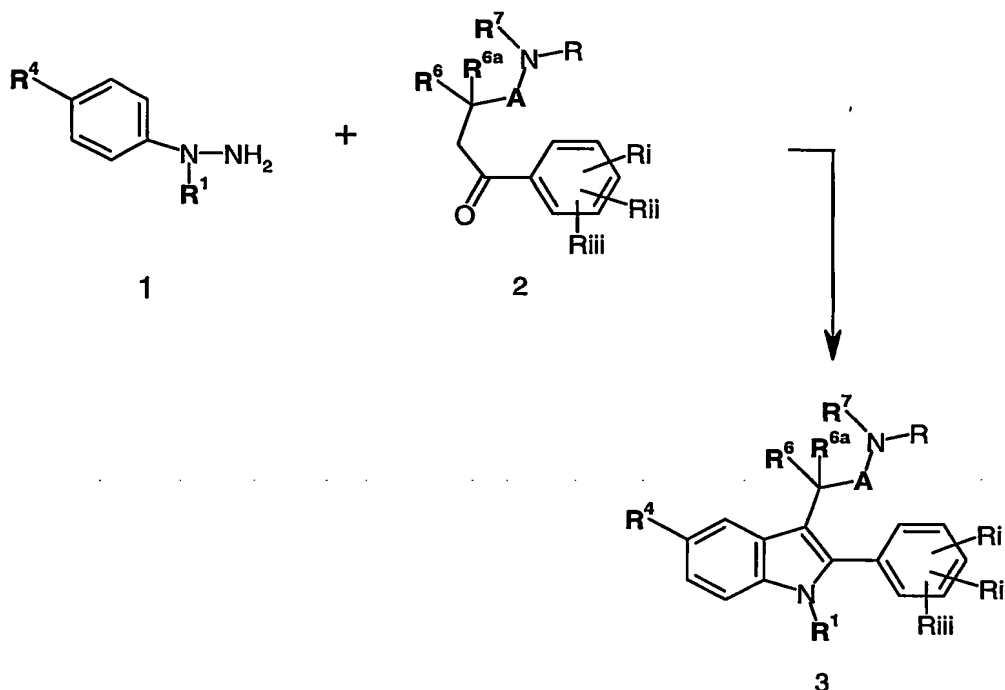
A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-  
5 protection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a  
10 suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by  
15 treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl  
20 group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group,  
25 for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

**EXPERIMENTAL****GENERAL REACTION SCHEMES**

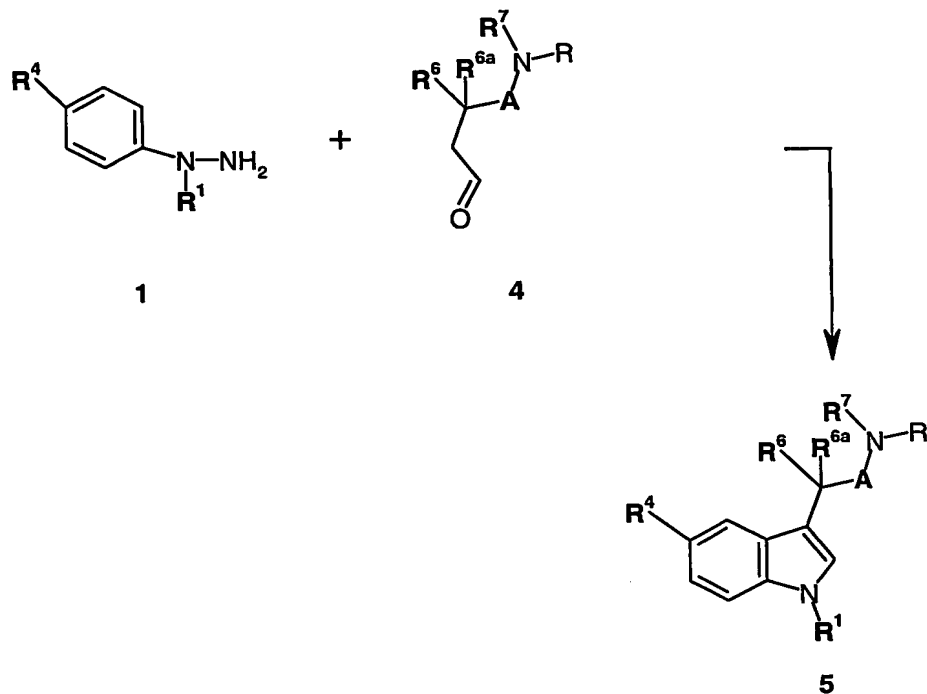
In the following schemes wherein Ri, Rii and Riii represent optional substituents on the phenyl ring which are optionally protected as necessary and R represents a protecting group, group  $R^2$  has been depicted as substituted phenyl for illustration purposes only. Other definitions of  $R^2$  are also appropriate.



Scheme a. - Fischer indole synthesis.

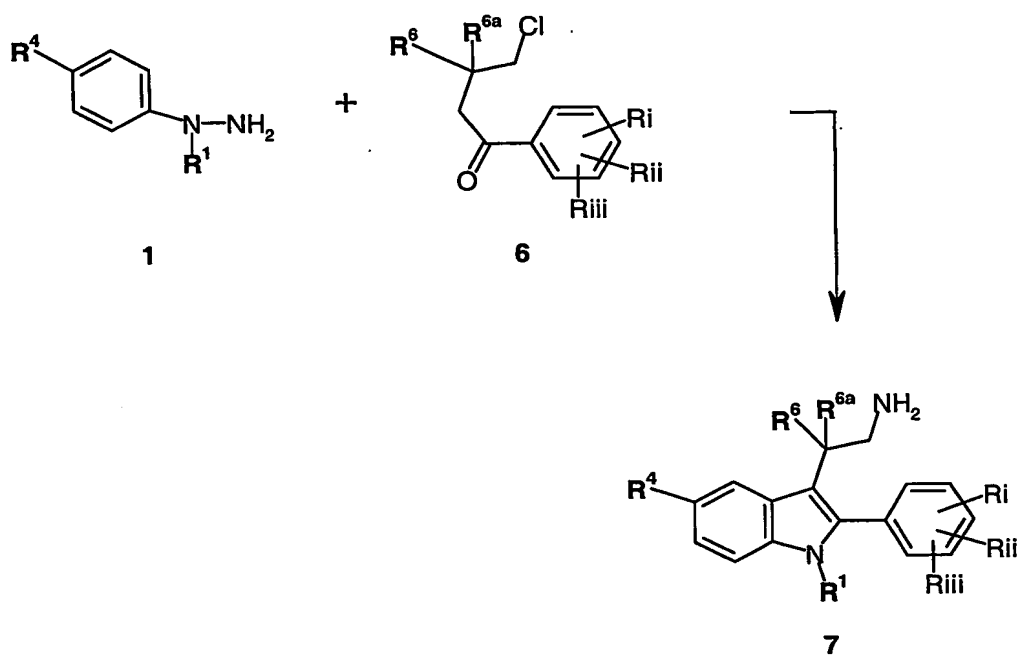
Tryptamines, such as 3 can be synthesised by the classic Fisher indole synthesis reaction by the condensation of a hydrazine 1 and a ketone 2, bearing hydrogen atoms  $\alpha$  to the carbonyl (Scheme a). Treatment of these reactants in a suitable solvent, such as acetic acid, ethanol, *tert*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. R represents a protecting group, eg *tert*-butylcarbamate or phthalimide.

- 23 -



Scheme b

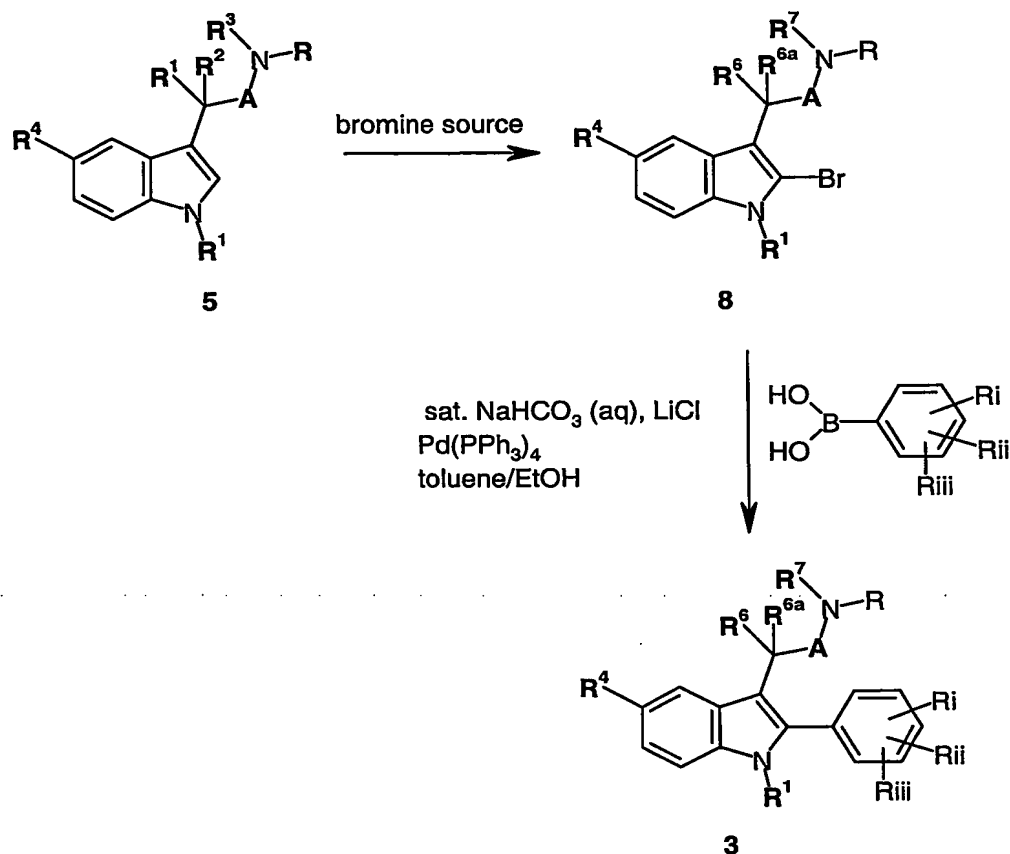
Tryptamines, such as represented in structure 5, can also be made using aldehydes 4, bearing hydrogen atoms  $\alpha$  to the carbonyl, by cyclization using the conditions above. In this case the substituent at the 2-position must be added later (see scheme d).



Scheme c

- 24 -

Tryptamine may also be synthesised utilising the Granburg reaction, wherein a tryptamine **1** is mixed with ketone **6**, bearing a chlorine atom  $\gamma$  to the carbonyl, and heated in a suitable solvent such as ethanol, *tert*-butanol, toluene at a temperature between 50 °C and 120 °C (Scheme c).

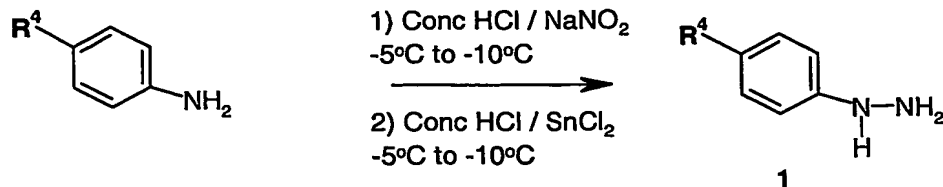


Scheme d

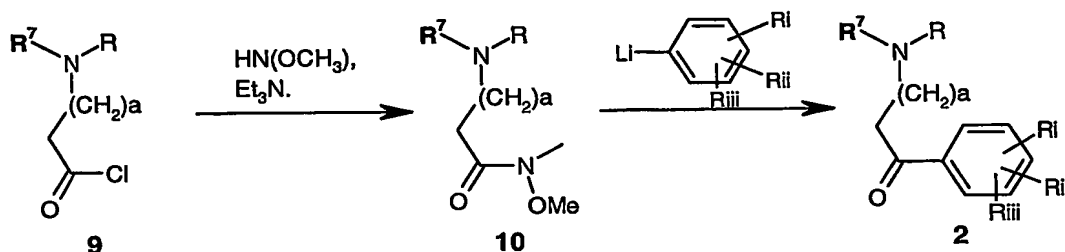
The tryptamine **5** can be treated with a 'bromine source', such as molecular bromide, pyridinium tribromide, pyrrolidone hydrobromide or polymer supported reagent equivalents, in an inert solvent such as chloroform, methylene chloride at -10 °C to 25 °C to yield the 2-bromo compound **8** (Scheme d). Reaction under Suzuki conditions with a palladium(0) catalyst, a weak base such aqueous sodium carbonate or saturated sodium hydrogen carbonate and the like, and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the desired compound **3**.



- 25 -

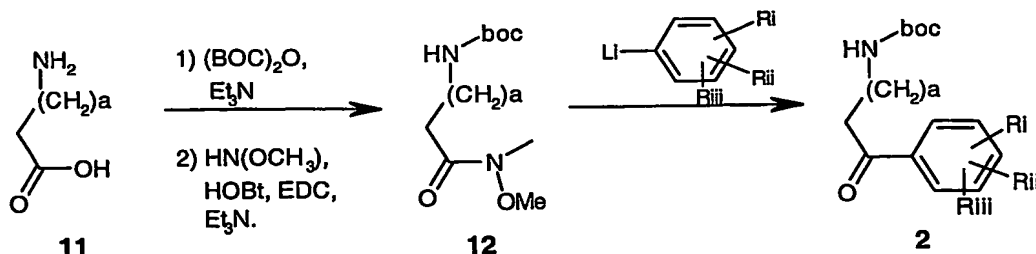


The hydrazines **1** can be purchased from commercial sources either as a free base or suitable salt (e.g. hydrochloride), which are both acceptable under the reaction conditions. Hydrazines may be synthesised by the two-step process of diazotisation of an aniline, under the preferred conditions of concentrated hydrochloric acid sodium nitrite at a temperature between -10 °C and -5 °C, then reduction under the preferred conditions of tin(II) chloride in concentrated hydrochloric acid at a temperature between -10 °C and -5 °C.



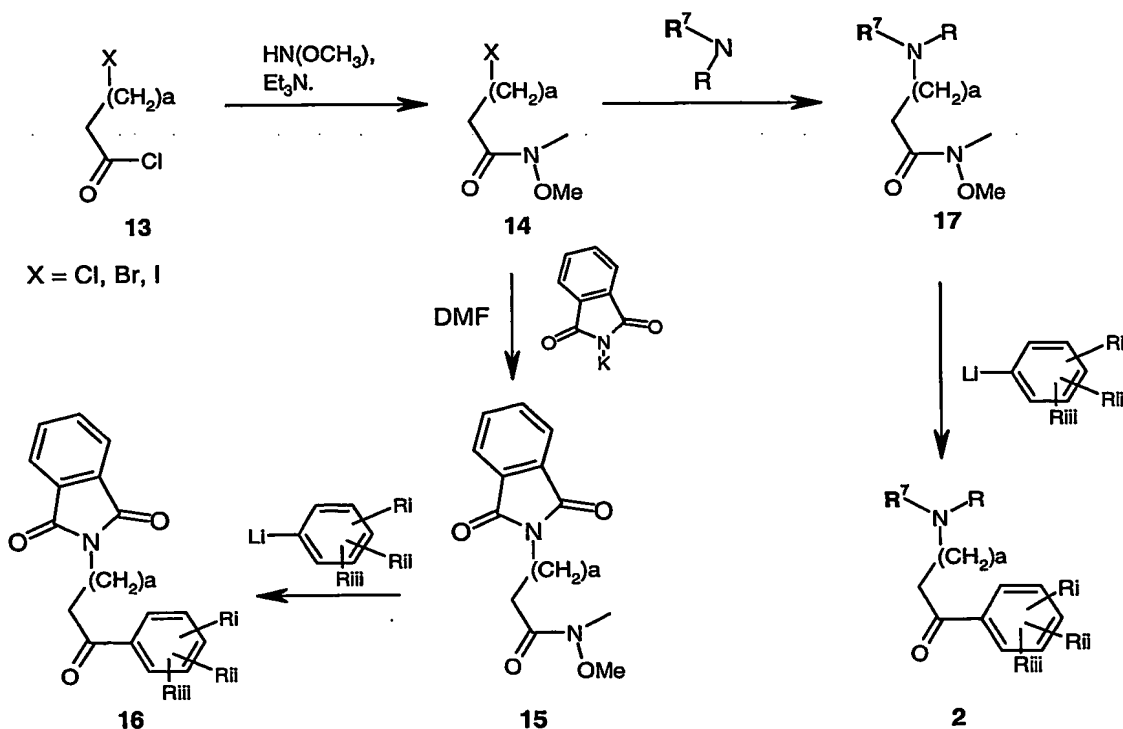
Scheme e.

Substituted ketones **2** can be prepared, as outlined in Scheme e starting from appropriate acid chlorides such as **9**. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine hydrochloride in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **10**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, 1988, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and 0 °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **2**.



Scheme f.

Commencing with a readily available amino acid with a suitable chain length [a] **11**, the nitrogen atom can be brought in at the beginning of the synthesis by the route shown in Scheme f. Protection of the amine group of **11** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl di-carbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C. Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 hours provided the corresponding coupled product **12**. Following the same route described above for scheme d, the aryl group can then be installed.

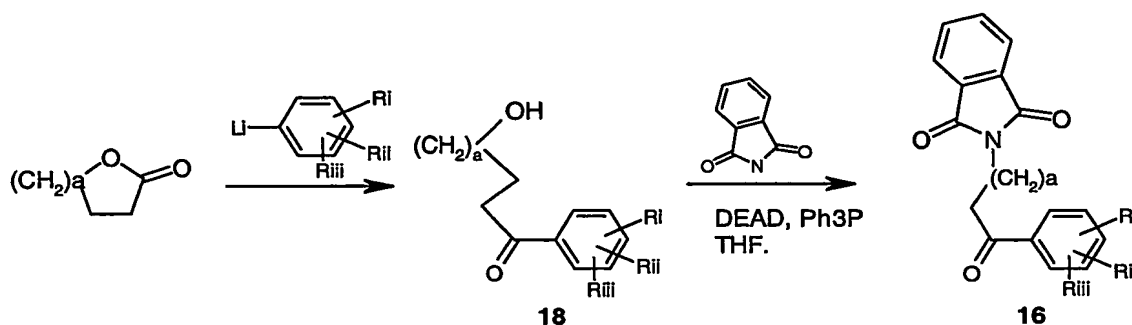


Scheme g.

Scheme g illustrates another method for the synthesis of ketone such as **2** and **16**, where the nitrogen group is introduced at a latter stage. As above a Weinreb amide **14** can be synthesised from an acid chloride. Treatment with the required amine, in an inert solvent such as THF, toluene, water and the such like can displace the group X to give **17**. As above the aryl group can be introduced by displacement of the Weinreb amide with a suitable aryl

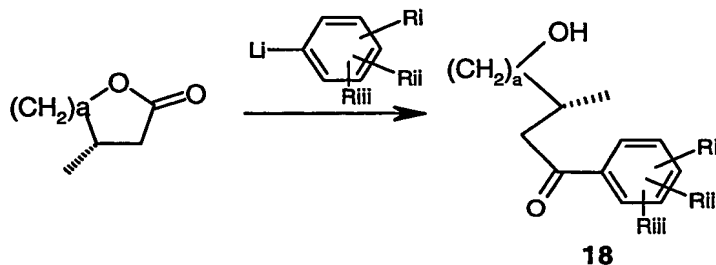
- 27 -

lithium nucleophile. Alternatively the nitrogen atom can be introduced already protected as a phthalimide by displacement of the group x by potassium phthalimide, or similar salt thereof, by heating in an inert polar solvent such as DMF, DMSO, THF, toluene with or without the presence of a catalyst such as tetrabutylammonium iodide and the such like, to yield the compound 15. Again displacement of the Weinreb amide with an organolithium species completes the synthesis of a ketone suitable for cyclization under the Fischer condition described above for indole synthesis.



Scheme h.

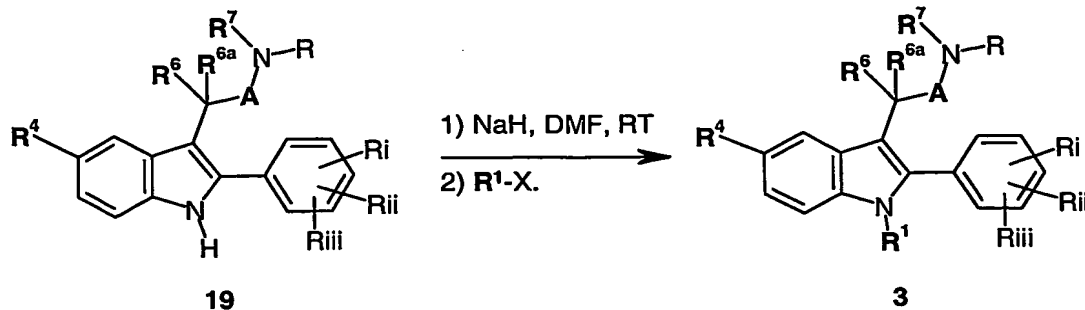
An alternative approach to a phthalimide protected nitrogen ketone, such as 16, can be taken by firstly treating a lactone, with an organolithium species as in the above schemes in a suitable solvent such as THF or ether at a low temperature of between  $-100^{\circ}\text{C}$  and  $-50^{\circ}\text{C}$  to yield a primary alcohol 18 (Scheme h). The hydroxyl function of 18 is replaced with a phthalimide group by a Mitsunobu reaction with an activating agent such as diethylazodicarboxylate (DEAD), diisopropylazodicarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the desired ketone 16.



Scheme h1

An analogous reaction to that described in Scheme h can be used to produce the respective intermediate required to introduce a  $\beta$ -methyl group at  $\text{R}^6$  in the final molecule (see Scheme h1).

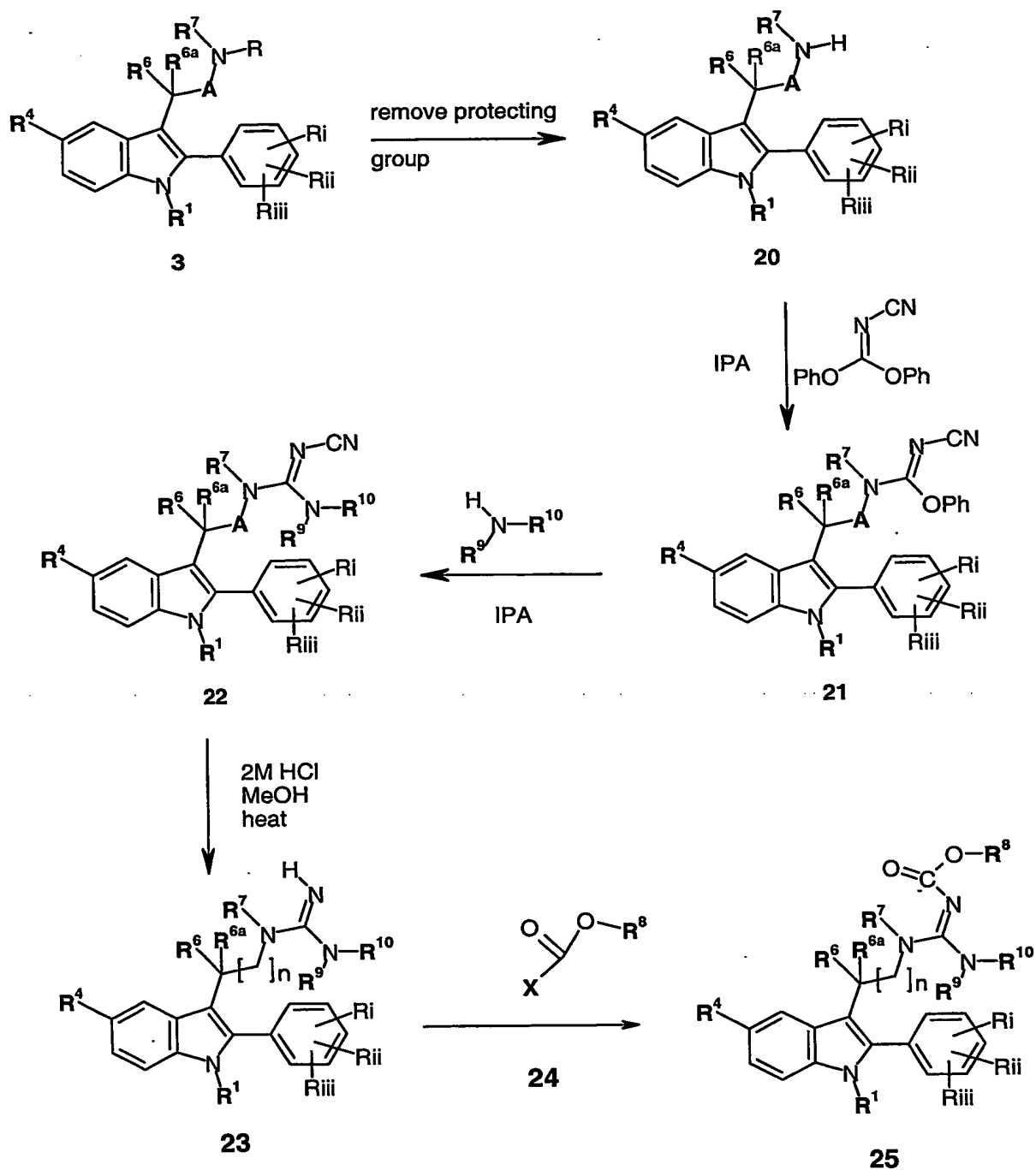
- 28 -



If the group  $\text{R}^1$  was not present on the starting hydrazine before cyclization to form an indole it may be added post cyclization by an alkylation reaction ( $\text{19} \rightarrow \text{3}$ ). The indole is de-

- 5 diisopropylamine, sodium hydroxide, potassium *tert*-butoxide in a suitable inert solvent such as THF, DMF, DMSO and the such like, and an alkyl halide added and the mixture stirred at a temperature between  $0^\circ\text{C}$  and room temperature.

- 29 -



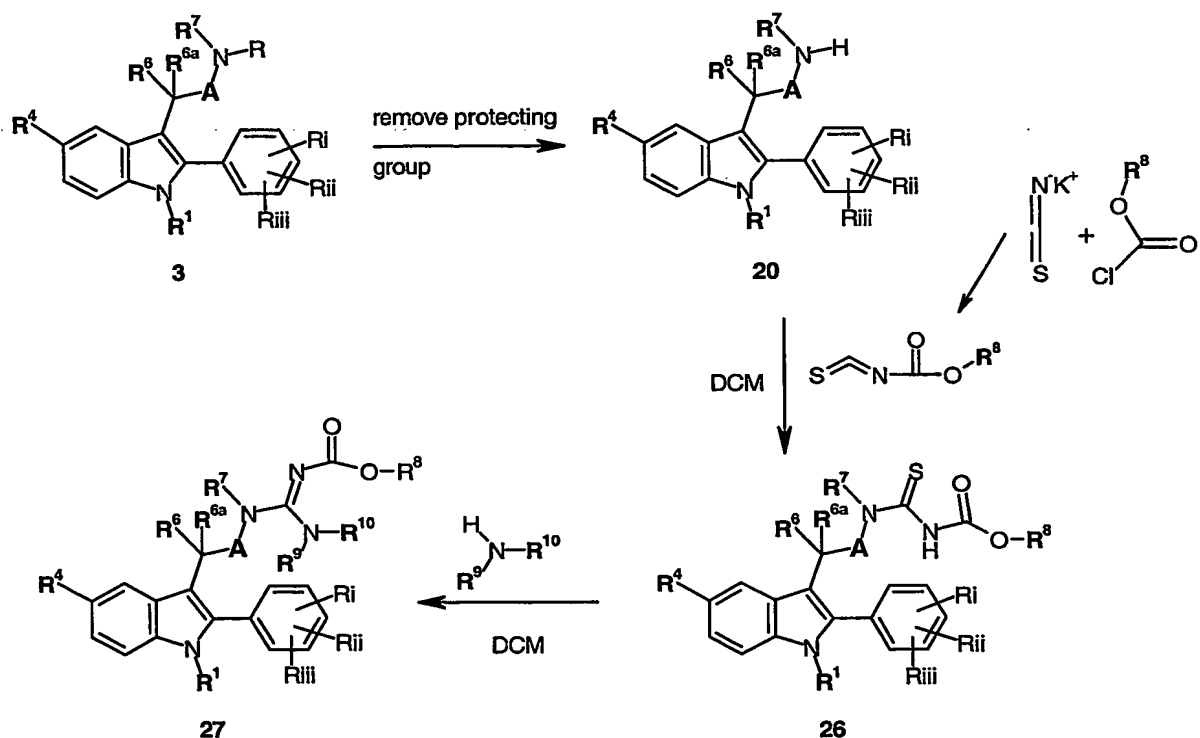
Scheme i

Depending on the route used above a tryptamine **20** suitable for conversion to a cyano-

5 butylcarbamate group was used then removal is accomplished using a strong acid, for example trifluoroacetic acid or hydrochloric acid in an inert solvent such as methylene chloride, chloroform, THF or dioxane at a temperature between  $-20^{\circ}\text{C}$  and  $25^{\circ}\text{C}$ . A

- 30 -

phthalimide group, for example, can be removed by hydrazine in a suitable solvent for example methanol, ethanol, methylene chloride, chloroform, THF dioxane at a temperature between -20°C and 25°C. The primary amine **20** can be converted to a cyano-guanidine **22** by the two step process of reaction with diphenyl cyanocarbonimidate in an inert organic solvent such as isopropyl alcohol, methylene chloride, chloroform, benzene, tetrahydrofuran and the like, at a temperature between -20°C and 50°C, followed by condensation with an appropriately substituted amine in an inert organic from the list above, with heating at a temperature between -20°C and 100°C (Scheme I **20**→**21**→**22**). Further treatment of **22** with 2 molar Hydrochloric acid in methanol at elevated temperature yields guanidine compounds **23**. **23** can then be reacted with a compound **24** wherein X is a leaving group such as p-nitrophenol, at a temperature of about 0°C in a suitable solvent such as DMF to form a compound **25**.



Scheme j

Alternatively, an alkyl chloroformate can be reacted with a solution of potassium thiocyanate in toluene/acetonitrile at about room temperature. The product of this reaction can then be reacted with tryptamine **20**, in dichloromethane (DCM) at 0°C to form **26**. **26** can

- 31 -

then be converted to 27 by reacting with the appropriate primary or secondary amine in the presence of EDC/DIPEA in dichloromethane at a temperature of about 0°C.

### EXAMPLES

5           The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

10           (ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear  
15 (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by  
20 thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keisegel: Art.9385);

(vii) isolate™ refers to silica (SiO<sub>2</sub>) based columns with irregular particles with an average size of 50µm with nominal 60 Å porosity [Source: Jones Chromatography, Ltd.,  
25 Glamorgan, Wales, United Kingdom].

### Abbreviations

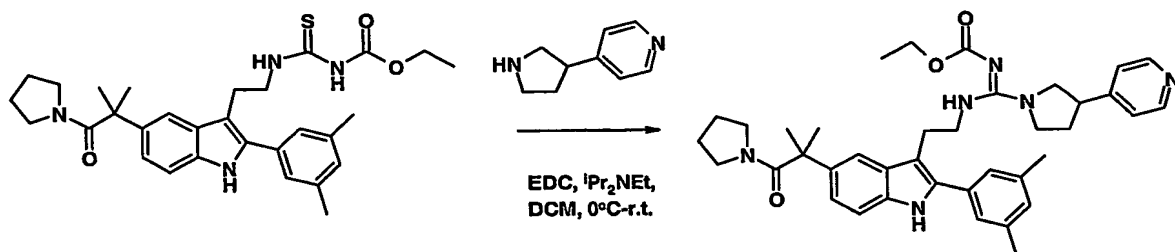
brine	a saturated solution of sodium chloride in distilled water
DCC	1,3-dicyclohexylcarbodiimide
30 DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIPEA	di-isopropylethylamine
DMSO	Dimethyl sulphoxide

- 32 -

DMF	dimethylformamide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenotriazole
5 THF	tetrahydrofuran

**Example 1**

**Ethyl (1E)-({2-[5-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-2-(3,5-dimethylphenyl)-1H-indol-3-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate**



10

5

Examples 1

To a stirred, cooled (0°C) solution of **5** (72mg, 0.13 mmol), 4-pyrrolidin-3-yl pyridine (30mg, 0.20 mmol) and N,N-diisopropylethylamine (46μl, 0.26 mmol) in DCM (3ml) was added EDC (52mg, 0.27 mmol). After stirring for 1hour at 0°C, the reaction mixture was stirred at ambient temperature for 16hours. The reaction was quenched by the addition of sodium bicarbonate (3ml, sat. aq.) and the phases were separated. The aqueous phase was extracted with DCM (2x 5ml), and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by chromatography on SiO<sub>2</sub>, eluting with a gradient 4-8% MeOH/DCM to give **8** as a yellow foam (20mg).

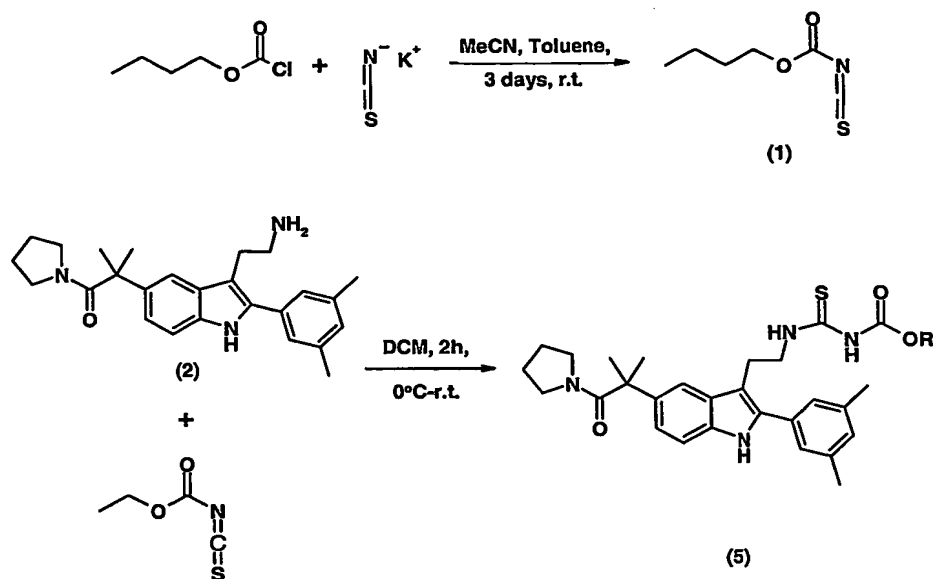
**Mass Spectrum** m/e 649.3 (M<sup>+</sup>+H).

**20 NMR Spectrum** (CDCl<sub>3</sub>, δ values) 1.28 (t, 3H), 1.47-1.79 (m, 10H), 1.88 (m, 1H), 2.19 (m, 1H), 1.35 (s, 6H), 2.76 (m, 2H), 3.13-3.42 (m, 6H), 3.44-3.59 (m, 4H), 3.62 (dd, 1H), 4.08 (q, 2H), 6.98 (s, 1H), 7.05 (m, 3H), 7.15 (s, 2H), 7.30 (d, 1H), 7.45 (s, 1H), 8.23 (s, 1H), 8.50 (d, 2H).



- 33 -

Starting materials were prepared as described in Scheme 1 below.



Scheme 1

(1)

5 n-Butyl chloroformate (2g, 14.64 mmol) was added to a stirred solution of potassium thiocyanate (7.83g, 80.57 mmol) in toluene (25ml) and acetonitrile (100ml) at ambient temperature. After stirring for 3 days the reaction mixture was filtered through a pad of celite and the filtrate reduced *in vacuo*. The residue was triturated with DCM/iso-hexane(1:1), filtered and the filtrate reduced *in vacuo*. The crude product was purified by chromatography  
10 on SiO<sub>2</sub>, eluting with DCM/iso-hexane(1:4) to give 1 as a yellow liquid (580mg).

<sup>1</sup>H NMR Spectrum (300MHz, CDCl<sub>3</sub>, δ values) 0.95 (m, 3H), 1.40 (m, 2H), 1.68 (m, 2H), 4.21 (t, 2H).

(5)

15 A solution of 2 (100mg, 0.25 mmol) in DCM (3 ml) was added to a stirred, cooled (0°C) solution of 1 (29μl, 0.25 mmol) in DCM (2 ml) under N<sub>2</sub>. The cooling bath was removed and stirring was continued for 2hours. The reaction was quenched by the addition of water (3 ml) and the phases were separated. The aqueous phase was extracted with DCM (2x 5ml), and the combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in*  
20 *vacuo* to give 5 as a white solid (144mg).

Mass Spectrum m/e 535.2 (M<sup>+</sup>+H).

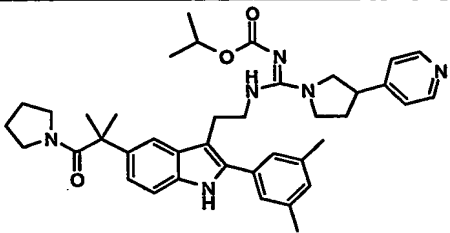
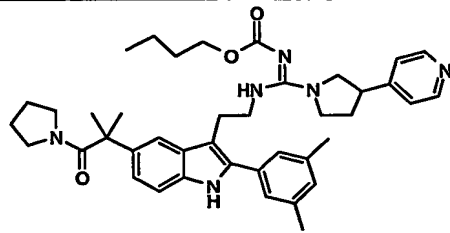
- 34 -

<sup>1</sup>H NMR Spectrum (300MHz, CDCl<sub>3</sub>, δ values) 1.20-1.36 (m, 3H), 1.48-1.83 (m, 10H), 2.40 (s, 6H), 2.80 (m, 2H), 3.28 (t, 2H), 3.55 (m, 2H), 3.95 (m, 2H), 4.08-4.24 (m, 2H), 6.99-7.09 (m, 2H), 7.20 (s, 2H), 7.24-7.35 (m, 1H), 7.65 (s, 1H), 7.97 (s, 1H), 8.20 (s, 1H), 9.70 (m, 1H).

5

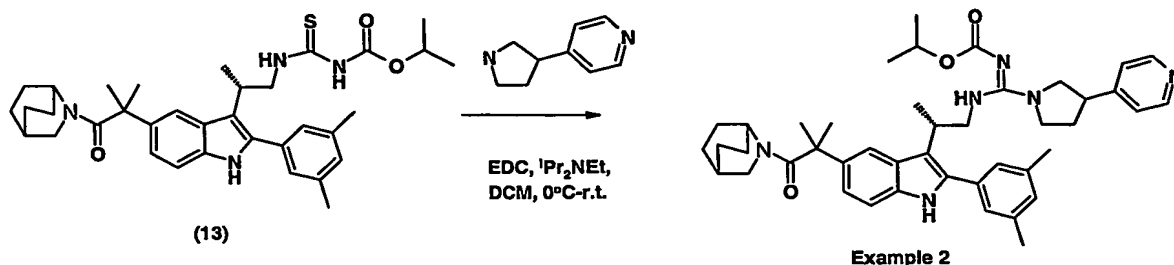
**Examples 1.1 – 1.2**

Following a procedure similar to that described in example 1, the following examples were prepared.

		<u>Mass Spectrum</u> m/e (M <sup>+</sup> +H)	<u>NMR Spectrum</u> (CDCl <sub>3</sub> , δ values)
1.1		661.5	1.25 (m, 6H), 1.54 (m, 2H), 1.56-1.74 (m, 8H), 1.88 (m, 1H), 2.18 (m, 1H), 2.35 (s, 6H), 2.76 (m, 2H), 3.12-3.40 (m, 6H), 3.42-3.58 (m, 4H), 3.63 (dd, 1H), 4.85 (m, 1H), 6.96 (s, 1H), 7.04 (d, 3H), 7.15 (s, 2H), 7.30 (d, 1H), 7.45 (s, 1H), 8.35 (s, 1H), 8.50 (d, 2H).
1.2		675.5	0.93 (t, 3H), 1.20-1.45 (m, 4H), 1.46-1.75 (m, 10H), 1.89 (m, 1H), 2.19 (m, 1H), 2.34 (s, 6H), 2.76 (m, 2H), 3.12-3.40 (m, 6H), 3.43-3.69 (m, 5H), 4.02 (m, 2H), 6.98 (s, 1H), 7.06 (d, 3H), 7.17 (s, 2H), 7.30 (m, 1H), 7.46 (s, 1H), 8.40 (s, 1H), 8.51 (d, 2H).

**Example 2**

isopropyl [(1E)-({(2S)-2-[5-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1H-indol-3-yl]propyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylene]carbamate



5

To a stirred, cooled (0°C) solution of **13** (543mg, 1.06 mmol), 4-pyrrolidin-3-yl pyridine (200mg, 1.35 mmol) and N,N-diisopropylethylamine (188μl, 1.08 mmol) in DCM (15ml) was added EDC (173mg, 0.90 mmol). After stirring for 16 hours at ambient temperature in the dark, the reaction mixture was cooled (0°C) and further N,N-diisopropylethylamine (94μl, 0.54 mmol) and EDC (86mg, 0.45 mmol) were added. The reaction mixture was stirred for 30 min at 0°C and 4 hours at ambient temperature. The reaction was quenched by the addition of water (15ml) and the phases were separated. The aqueous phase was extracted with DCM (2x 10ml), and the combined organic layers were washed with brine (10ml, sat. aq.), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by chromatography on SiO<sub>2</sub>, eluting with a gradient of 5-7% MeOH/DCM to give **Example 2** as a yellow foam (266mg).

10

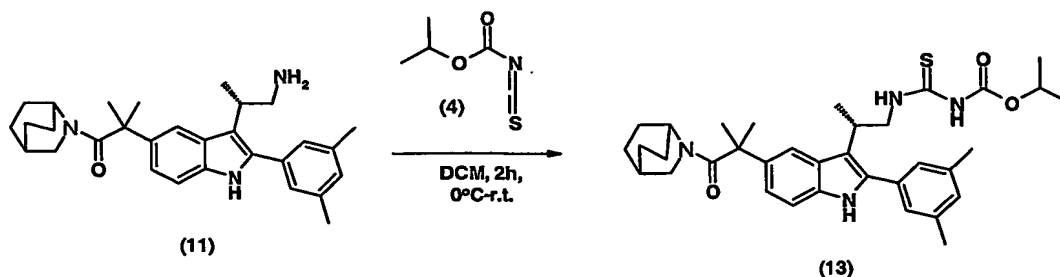
15

Mass Spectrum m/e 715.3 (M<sup>+</sup>-H).

NMR Spectrum (CDCl<sub>3</sub>, δ values) 1.20-1.39 (m, 10H), 1.40-1.70 (m, 14H), 1.72-1.93 (m, 1H), 2.14 (m, 1H), 2.35 (s, 6H), 3.20-3.70 (m, 11H), 4.83 (m, 1H), 6.95-7.10 (m, 6H), 7.32 (d, 1H), 7.48 (s, 1H), 8.02 (s, 1H), 8.50 (d, 2H).

20

Starting materials were prepared as described in Scheme 2 below.



Scheme 2

**(13)**

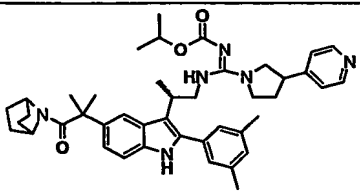
A solution of **11** (412mg, 0.90 mmol) in DCM (7 ml) was added to a stirred, cooled (0°C) solution of **4** (131mg, 0.90 mmol) in DCM (8 ml) under N<sub>2</sub>. The cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched by the addition of water (10 ml) and the phases were separated. The aqueous phase was extracted with DCM (2x 10ml), and the combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give **13** as a yellow solid (573mg).

Mass Spectrum m/e 603.3 (M<sup>+</sup>+H).

- 10 NMR Spectrum (CDCl<sub>3</sub>, δ values) 1.18-1.67 (m, 24H), 2.38 (s, 6H), 3.45 (s, 2H), 3.55 (m, 1H), 4.00 (m, 1H), 4.14 (m, 2H), 4.86(m, 1H), 7.01-7.10 (m, 2H), 7.14 (s, 2H), 7.32 (d, 1H), 7.56 (s, 1H), 7.73 (s, 1H), 7.96(s, 1H), 9.55 (m, 1H).

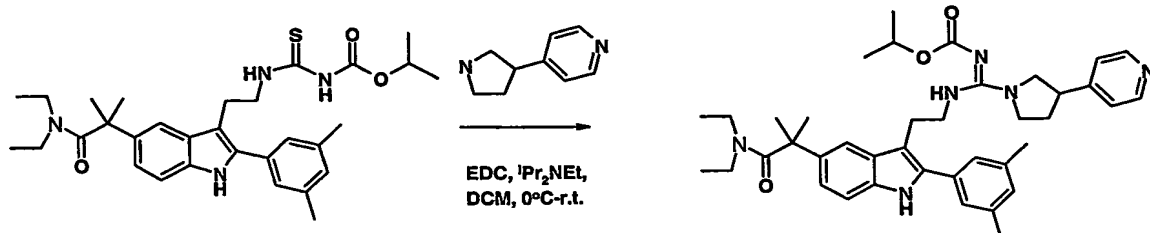
**Example 2.1**

- 15 Following a procedure similar to that described in Example 2, the following example was prepared.

		<u>Mass Spectrum</u> m/e (M <sup>+</sup> -H)	<u>NMR Spectrum</u> (CDCl <sub>3</sub> , δ values)
2.1		701.2	1.00-1.40 (m, 10H), 1.42-1.95 (m, 14H), 2.15 (m, 1H), 2.35 (s, 6H), 3.20-3.80 (m, 9H), 4.55-4.90 (m, 2H), 6.99-7.12 (m, 5H), 7.15 (d, 1H), 7.32 (d, 1H), 7.55 (s, 1H), 8.05 (s, 1H), 8.50 (d, 2H).

**Example 3**

**Isopropyl (1*E*)-((2-[5-(1,1-dimethyl-2-oxo-2-(*N,N*-diethylamino)ethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]ethyl)amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate**



(19)

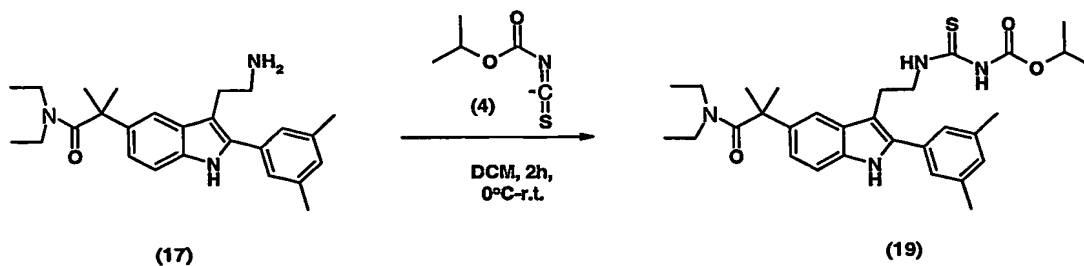
Example 3

To a stirred, cooled (0°C) solution of **19** (584mg, 1.06 mmol), 4-pyrrolidin-3-yl pyridine (236mg, 1.59 mmol) and *N,N*-diisopropylethylamine (277μl, 1.59 mmol) in DCM (15ml) was added EDC (204mg, 1.06 mmol). After stirring for 16 hours at ambient temperature in the dark, the reaction mixture was cooled (0°C) and further *N,N*-diisopropylethylamine (185μl, 1.06 mmol) and EDC (102mg, 0.53 mmol) were added. The reaction mixture was stirred for 30 minutes at 0°C and 4 hours at ambient temperature. The reaction was quenched by the addition of water (15ml) and the phases were separated. The aqueous phase was extracted with DCM (2x 10ml), and the combined organic layers were washed with brine (10ml, sat. aq.), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by chromatography on SiO<sub>2</sub>, eluting with a gradient of 5-7% MeOH/DCM to give **21** as a pale yellow foam (420mg).

**Mass Spectrum** *m/e* 663.4 (*M*<sup>+</sup>-H).

**NMR Spectrum** (CDCl<sub>3</sub>, δ values) 0.70 (m, 3H), 1.13 (m, 3H), 1.26 (dd, 6H), 1.60 (s, 6H), 1.88 (m, 1H), 2.18 (m, 1H), 2.34 (s, 6H), 2.92 (m, 2H), 3.13-3.44 (m, 8H), 3.50 (m, 2H), 3.63 (dd, 1H), 4.85 (m, 1H), 6.96 (s, 1H), 7.04 (d, 3H), 7.16 (s, 2H), 7.30 (d, 1H), 7.41 (s, 1H), 8.30 (s, 1H), 8.50 (d, 2H).

Starting materials were prepared as described in Scheme 3 below.



(17)

(19)

## Scheme 3

**(19)**

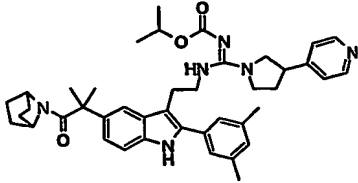
A solution of **17** (190mg, 0.47 mmol) in DCM (7 ml) was added to a stirred, cooled (0°C) solution of **4** (68mg, 0.47 mmol) in DCM (3 ml) under N<sub>2</sub>. The cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched by the addition of water (10 ml) and the phases were separated. The aqueous phase was extracted with DCM (2x 10ml), and the combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give **19** as a yellow solid (260mg).

10 Mass Spectrum m/e 551.2 (M<sup>+</sup>+H).

NMR Spectrum (CDCl<sub>3</sub>, δ values) 0.71 (m, 3H), 1.13 (m, 3H), 1.27 (d, 6H), 1.63 (s, 6H), 2.40 (s, 6H), 2.95 (m, 2H), 3.26(t, 2H), 3.36 (m, 2H), 3.95 (m, 2H), 4.90 (m, 1H), 7.00-7.06 (m, 2H), 7.20 (s, 2H), 7.30 (d, 1H), 7.61 (s, 1H), 7.83 (s, 1H), 8.07 (s, 1H), 9.72 (m, 1H).

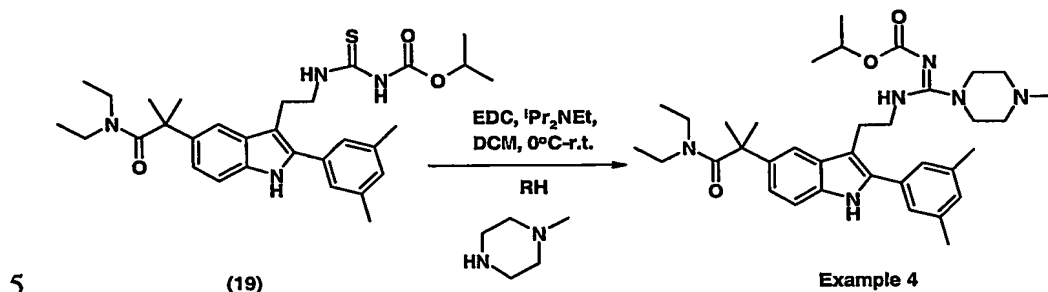
15 **Example 3.1**

Following a procedure similar to that described in Example 3, the following example was prepared.

		<u>Mass Spectrum</u> m/e (M <sup>+</sup> H)	<u>NMR Spectrum</u> (CDCl <sub>3</sub> , δ values)
3.1		687.3	1.00-1.80 (m, 8H), 1.27 (d, 6H), 1.60 (d, 6H), 1.90 (m, 1H), 2.20 (m, 1H), 2.35 (s, 6H), 3.14-3.80 (m, 10H), 4.60-4.80 (m, 1H), 4.85 (m, 1H), 6.99 (s, 1H), 7.05 (d, 2H), 7.10-7.19 (m, 3H), 7.30 (d, 1H), 7.49 (s, 1H), 8.10 (s, 1H), 8.54 (d, 2H).

**Example 4**

**Isopropyl (1*E*)-({2-[5-[2-(*N,N*-diethylamino)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]ethyl}amino)(4-methylpiperazin-1-yl)methylidenecarbamate**



To a stirred, cooled (0°C) solution of **19** [see Example 3] (217mg, 0.39 mmol), *N*-methylpiperazine (66μl, 0.59 mmol) and *N,N*-diisopropylethylamine (82μl, 0.47 mmol) in DCM (4ml) was added EDC (76mg, 0.40 mmol). After stirring for 16hours at ambient

10 temperature, the reaction mixture was cooled (0°C) and further *N,N*-diisopropylethylamine (41μl, 0.24 mmol) and EDC (38mg, 0.20 mmol) were added. The reaction mixture was stirred for 30 minutes at 0°C and 4hours at ambient temperature. The reaction was quenched by the addition of water (10ml) and the phases were separated. The aqueous phase was extracted with DCM (2x 10ml), and the combined organic layers were washed with brine

15 (5ml, sat. aq.), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by chromatography on SiO<sub>2</sub>, eluting with a gradient of 2-10% MeOH/DCM to give **23** as a white solid (130mg).

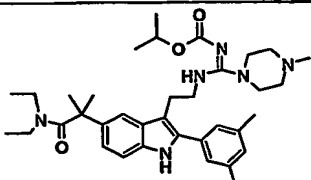
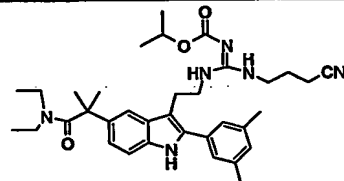
**Mass Spectrum** *m/e* 617.5 (*M*<sup>+</sup>+*H*).

**NMR Spectrum** (CDCl<sub>3</sub>, δ values) 0.74 (m, 3H), 1.15 (m, 3H), 1.28 (d, 6H), 1.62 (s, 6H),

20 2.23 (s, 3H), 2.27 (t, 4H), 2.40 (s, 6H), 2.93 (m, 2H), 3.19 (m, 2H), 3.25 (t, 4H), 3.39 (m, 4H), 4.86 (m, 1H), 7.05 (m, 2H), 7.15 (s, 2H), 7.32 (d, 1H), 7.43 (s, 1H), 8.05 (s, 1H), 8.19 (m, 1H).

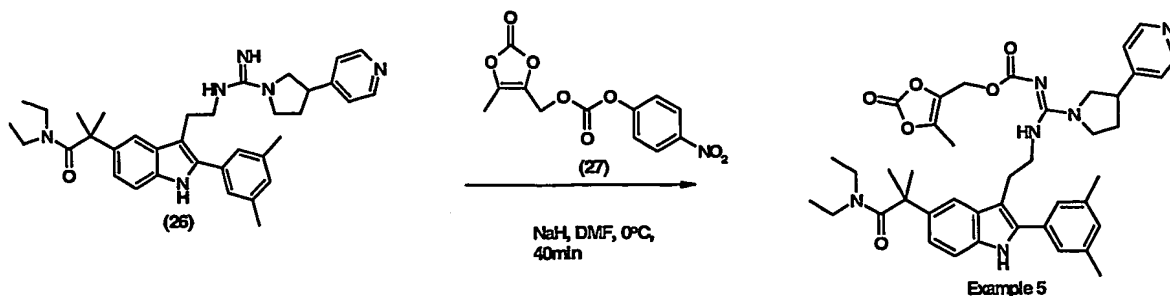
**Examples 4.1 – 4.2**

Following a procedure similar to that described in Example 4, the following examples were prepared.

		<u>Mass Spectrum</u> m/e (M <sup>+</sup> +H)	<u>NMR Spectrum</u> (CDCl <sub>3</sub> , δ values)
4.1		627.3	0.72 (m, 3H), 1.14 (m, 3H), 1.27 (d, 6H), 1.55-1.70 (m, 8H), 1.78 (m, 2H), 2.40 (s, 6H), 2.70 (m, 1H), 2.93 (m, 2H), 3.02-3.24 (m, 4H), 3.38 (m, 6H), 4.86 (m, 1H), 7.07 (m, 2H), 7.15 (s, 2H), 7.33 (d, 1H), 7.40 (s, 1H), 8.14 (s, 1H), 8.35 (s, 1H).
4.2		601.8	0.74 (m, 3H), 1.14 (m, 3H), 1.25 (d, 6H), 1.49 (m, 2H), 1.60 (s, 6H), 2.10 (m, 2H), 2.38 (s, 6H), 2.83-3.10 (m, 4H), 3.18 (t, 2H), 3.38 (m, 2H), 3.54 (m, 2H), 4.85 (m, 1H), 7.03 (s, 1H), 7.09 (d, 1H), 7.16 (s, 2H), 7.35 (d, 1H), 7.43 (s, 1H), 8.19 (s, 1H).

**5 Example 5**

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl (1*E*)-({2-[5-[2-(diethylamino)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate





- 41 -

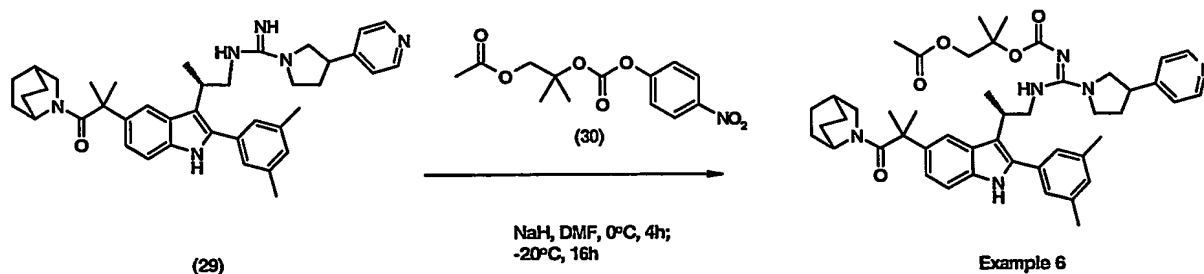
To a cooled (0°C), stirred solution of (26) (118mg, 0.19 mmol) in DMF (3ml), under N<sub>2</sub>, was added NaH (16mg, 0.40 mmol). After stirring for 30minutes, a solution of 27 (62mg, 0.21 mmol) in DMF (2ml) was added dropwise. The reaction mixture was stirred at 0°C for 4hours and left to stand at -20°C for 16hours. The reaction was quenched by the addition of water (15ml) and then extracted with EtOAc (3 x 10ml). The combined organic layers were washed with brine (10ml sat. aq.), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by chromatography on SiO<sub>2</sub>, eluting with a gradient of 2-10% MeOH/DCM to give 28 as a yellow solid (45mg).

Mass Spectrum m/e 733.3 (M<sup>+</sup>-H).

10 NMR Spectrum (CDCl<sub>3</sub>, δ values) 0.73 (m, 3H), 1.14 (m, 3H), 1.60 (s, 6H), 1.90 (m, 1H), 2.10 (s, 3H), 2.22 (m, 1H), 2.35 (s, 6H), 2.90 (m, 2H), 3.14-3.62 (m, 11H), 4.79 (s, 2H), 6.99 (s, 1H), 7.00-7.12 (m, 3H), 7.17 (s, 2H), 7.34 (d, 1H), 7.41 (s, 1H), 8.05 (s, 1H), 8.54 (m, 2H).

### Example 6

15 2-[[[[(1E)-({(2S)-2-[5-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1H-indol-3-yl]propyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylene]amino}carbonyl)oxy]-2-methylpropyl acetate



To a cooled (0°C), stirred solution of (29) (50mg, 74.9 μmol) in DMF (2ml), under N<sub>2</sub>, was added NaH (7mg, 0.16 mmol). After stirring for 30minutes a solution of (30) (67mg, 0.23 mmol) in DMF (2ml) was added dropwise. The reaction mixture was stirred at 0°C for 40minutes. The reaction was quenched by the addition of water (15ml) and then extracted with EtOAc (3 x 10ml). The combined organic layers were washed with brine (10ml sat. aq.), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by chromatography on SiO<sub>2</sub>, eluting with a gradient of 5-10% MeOH/DCM to give 31 as a yellow solid (10mg).

Mass Spectrum m/e 789.3 (M<sup>+</sup>+H).

- 42 -

NMR Spectrum (CDCl<sub>3</sub>,  $\delta$  values) 1.10-1.70 (m, 24H), 1.75-1.90 (m, 1H), 2.00 (s, 3H), 2.15-2.30 (m, 1H), 2.30 (s, 6H), 3.17 (m, 1H), 3.28-4.00 (m, 12H), 6.86(s, 2H), 6.95-7.15 (m, 3H), 7.20-7.30 (m, 2H), 7.46 (s, 1H), 8.18 (d, 1H), 8.50 (d, 2H).

## 5 THERAPEUTIC USES

Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The  
10 formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra  
15 alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of  
20 0.1mgkg<sup>-1</sup> to 30mgkg<sup>-1</sup> (preferably, 5mgkg<sup>-1</sup> to 20mgkg<sup>-1</sup>) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the  
25 composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene  
30 glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl  $\beta$  cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this

- 43 -

respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatic cancer, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

- i) anti-angiogenic agents (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);
- ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone  $5\alpha$ -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies,

- 44 -

growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

- iii) biological response modifiers (for example interferon);
- iv) antibodies (for example edrecolomab); and
- 5 v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example
- 10 cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide,
- 15 amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or radiotherapy.

### ASSAYS

- 20 The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

#### Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer
- 25 (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4<sup>0</sup> C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.
- 30 From this data, the IC<sub>50</sub> of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

- 45 -

Compounds according to the present invention have activity at a concentration from 1nM to 5  $\mu$ M.

#### Binding Assay Using Human GnRH Receptor

- 5        Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC<sub>50</sub> which is the compound concentration required to inhibit the specific binding of [<sup>125</sup>I]buserelin to GnRH receptors by 50%. [<sup>125</sup>I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

10

#### Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

#### 15 Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS).

20 The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
- 25 4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
- 30 6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;

- 46 -

8. Re-suspension of the cells in culture medium of DMEM containing 0.37%  $\text{NaHCO}_3$ , 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the  
5 collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of  $3 \times 10^5$  cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5%  $\text{CO}_2$ /95% air atmosphere at  $37^\circ\text{C}$  for 3 to 4 days

#### 10 Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

- 1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37%  $\text{NaHCO}_3$ , 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids  
15 (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

- Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one  
20 compound), these are added to other respective duplicate wells. Incubation is then carried out at  $37^\circ\text{C}$  for three hours.

- Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at  $2000 \times g$  for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno  
25 assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5  $\mu\text{M}$ .